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I. THE RÔLE OF THE SALIVARY GLANDS IN
THE THIRST MECHANISM

II. THE INFLUENCE OF ATROPINE AND
PILOCARPINE ON THIRST
(VOLUNTARY INGESTION OF WATER)

A DISSERTATION SUBMITTED TO THE
GRADUATE FACULTY IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

By
MARY FREYER MONTGOMERY

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THE RÔLE OF THE SALIVARY GLANDS IN THE THIRST MECHANISM

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From the Department of Physiology of the University of Chicago

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Two main theories have been advanced to explain the mechanism of the sensation of thirst. According to one, thirst is a general bodily sensation; the other states that the sensation of thirst originates locally in the mouth and pharynx. In his article, "The Physiological Basis of Thirst," Cannon (1) summarizes the early evidence for the two theories.

1. *The theory that thirst is a general sensation.* According to Schiff, thirst arises as a result of a lowering of the water content of the body. The feeling of dryness in the throat is secondary and the local reference to the pharynx is due to the association of experiences. Evidence commonly cited in support of this theory is the following:

Intravenous injections in dogs and man abolish the desire to drink (Dupuytren, Orfila, Magendie). Claude Bernard noted that a dog with a gastric fistula continued to drink until fatigued. Mayer (2) found that in thirsting animals there was an increase in the osmotic pressure of the blood. His explanation of thirst was that the excitation produced by the blood with abnormal molecular concentration is transmitted (by sensory nerves from the blood vessels) to a medullary center controlling the vascular changes which regulate the osmotic pressure of the blood. The general disturbance of the whole body leads to malaise and a sensation of dryness in the pharynx accompanied by a desire to drink. Wettendorf (3) found that dogs might give evidence of thirst before their blood became hypertonic and that a dog can apparently quench his thirst with normal salt solution without lowering the osmotic pressure of the blood. Wettendorf ascribed the origin of thirst not to changes in blood concentration and their influence upon the central nervous system, but to withdrawal of water from the tissues.

2. *The theory that thirst is a sensation of local origin.* In 1885 Lepidichioti and Fubini abolished thirst in a patient with marked polyuria by brushing the throat with a weak solution of cocaine, the effect persisting 15 to 35 minutes. Valenti, in 1910, cocainized the upper part of the esophagus of thirsting dogs and noted that they refused drink although still able to swallow.

In seeking to explain the thirst mechanism, Cannon first calls attention to the dryness of the mouth and throat which is emphasized in accounts of severe thirst, such as that given by King (4). The symptoms described were absence of the salivary and mucous secretions, parched mouths and throats, and inability to swallow dry food, as well as dimness of vision, deafness, tottering gait, delirium, dyspnea, and a feeling of suffocation. However, King also states: "The sensibility of the lingual and buccal mucous membranes was so much impaired that they could not perceive when anything was in their mouth," yet one is led to believe that thirst was present to an extreme degree. The importance of the glands of the mouth and pharynx in keeping the mucous membrane moist, and thus preventing thirst, has been asserted by Weber (5), who was of the opinion that a diminution of the water content of the blood might decrease the secretions upon the mucous surfaces and so lead to thirst. Ludwig (6) and Schaefer (7) expressed similar views. Cannon, in particular, has emphasized this view. He advances the theory that the salivary glands are responsive to the state of hydration of the body, and that when, for any reason, they fail to secrete sufficiently, thirst develops, due to local dryness of the mouth and pharynx.

It has been shown that reflex secretion of saliva tends to occur under conditions which cause dryness of the mouth, such as dry food (Pavlov, 8), and breathing with the mouth open (Zebrowski, 9). Cannon, working on himself, induced thirst by sweating and abstaining from water. He found that he produced less saliva when thirsty than when not thirsty, and that the relationship between the salivary flow and the sensation of thirst was definite. Boring (10) made similar experiments, his results agreeing in the main with Cannon's. However, one subject noted the onset of thirst before any marked decrease in the amount of the salivary secretion. Cannon also tried the effect of atropine, and while under its influence, "experienced all the symptoms of thirst." Rinsing the mouth with weak novocaine abolished thirst; he did not drink, and yet thirst disappeared when the atropine effect wore off.

Additional evidence in support of Cannon's point of view has appeared since his original article was written. Pack (11) deprived rabbits of water for seven days. Profuse salivation was then induced in some of the animals by means of pilocarpine and these animals were observed to drink less than the rabbits which had received no pilocarpine. Gantt (12) has shown that both the unconditioned and the food conditioned reflex secretion of the parotid and submaxillary glands in children is diminished after a period of water deprivation. Crisler (13) reports that in dogs the conditioned reflex salivary secretion developed by morphine was diminished in quantity during periods of dehydration.

Some writers consider marked dryness of the mouth and pharynx as

synonymous with thirst, Cannon (1), Siebeck (14), Meyer (15), but Mueller (16), in particular, asserts that dryness of the mouth is a sensation distinct from true thirst. He states that in his experiments on man dryness due to mouth breathing and atropine are not like thirst. Desire for water can be experienced while the mouth is still wet, and mere wetting of the mouth does not give relief. Severe thirst may occur in nephritics and in cardiac patients who have retention of water in the tissues as edema, and be relieved at the onset of diuresis. Wier, Larson, and Rowntree (17) tested out the relationship of dryness of the mouth to thirst in nine patients with diabetes insipidus. They painted the patients' throats with a weak solution of cocaine to the point of anesthesia without being able to control either the polydypsia or the polyuria. Neither did pilocarpine pushed to the point of salivation (in 4 cases) relieve the intense thirst. Three of the nine patients gave a definite history of the onset of thirst before the onset of their polyuria, that is, before any marked loss of fluid from the body had occurred. Wier, Larson and Rowntree, therefore, conclude that in diabetes insipidus thirst is more than a local sensation due to dryness of the mouth and throat.

One finds additional evidence that thirst is not dependent upon the absence of the salivary secretions from cases in which the salivary glands are either congenitally absent, or for some reason have ceased to secrete saliva. The reports of such cases emphasize the very dry condition of the mouth, and the necessity for taking fluids along with the food to facilitate swallowing, but no mention is made of increased desire for water, which should have been present if the salivary glands were truly so important in regulating the water intake. It appeared possible to make a crucial test of the importance of the salivary secretion in the control of water ingestion by completely extirpating the salivary glands. If, indeed, a diminished secretion of saliva leads to local dryness of the mouth, which in turn causes the animal to drink, a total elimination of the salivary secretion should produce an increase in the daily ingestion of water by the animal.

Bidder and Schmidt (quoted by Cannon) tied off the ducts of all the salivary glands in dogs and noted that the layer of fluid on the buccal mucosa was much diminished and that the desire for water was enormously increased. Extirpation of one or more of the salivary glands in animals has been done by a large number of workers. Budge, in 1842, extirpated the parotid, submaxillary and sublingual glands in dogs. However, the dog, in common with all carnivores and rodents, possesses on each side, beneath the zygomatic arch, another mucous gland, the orbital gland, which is about the size of the submaxillary. Fehr (18) was the first to extirpate the salivary glands completely in dogs. He stated that the animals drank a little more water than before, presumably to increase the ease of chewing and swallowing, but he gave no measurements of fluid

intake before and after operation. Minkowski (19) also extirpated all eight glands in dogs, but made no mention of an increased fluid intake after the operation.

METHODS. In these experiments, the supposed relationship of the salivary secretion to the preservation of the moist condition of the oral mucous membranes and to the prevention of thirst was put to a test by extirpation of all eight glands in dogs. The animals were placed upon a diet of raw or partially cooked meat and bread, to which was added water or milk in proportions which will be indicated later in this article. This was done to insure a diet moist enough to avoid the possibility that the animals might drink water merely to wash down their food, as Fehr thought was the case in his experiments. The animals were permitted to drink water as they desired, since the purpose of the experiment was to note any spontaneous development of thirst after extirpation of the salivary glands. The water drunk, the water content of the food, the amount of food eaten, and the urine output were recorded.

The salivary glands were removed in three to four operations. In this way there was only slight disturbance of the usual food and fluid intake. Sometimes the dog would even eat and drink as usual on the day of the operation. The parotid, submaxillary and sublingual glands of one side were removed at one operation. After a recovery period of six to ten days the glands of the opposite side were extirpated. The orbital glands were usually removed one at a time at different operations, since the local swelling resulting from this operation is considerable. However, an orbital gland may conveniently be removed at the same operation with the other salivary glands of the same side. The parotid was dissected out carefully, the facial nerve being preserved. In the case of the orbital gland, removal was effected through an incision through the masseter muscle parallel with and just inferior to the zygomatic arch. This was the approach described and used by Fehr for his original extirpation of the gland. In some instances considerable post-operative swelling was noted, but recovery was rapid.

Six animals were observed in all. For convenience in discussion they are divided into two groups of three dogs each. Of the original group of three animals, two are still under observation one year from the time of the final operation. Although they have been used for other experimental work, observation on their fluid intake has been made from time to time. The third was used for other work and was killed one year from the time of the final operation. The conclusions stated in this article are based chiefly upon the findings in these three animals. About eight months ago, Miss Dorothy Palmer, working in this department, kindly permitted me to observe the fluid intake on three of her dogs whose salivary glands were removed. These will be referred to as group II.

The three male dogs in group I (dogs 3, 4 and 7), weighing 6.3 to 9.1 kgm., were placed on a diet of equal parts of raw or slightly cooked lean meat and baker's bread, and some bone meal. All of them ate greedily at first, but after they had gained in weight, they spontaneously reduced their food intake, and after this had occurred, less food was offered them. With minor variations their food intake remained at this level throughout the period of observation. When they failed to eat all the food offered, the meat was always eaten and the bread refused. Allowance is made for this in the calculation of the water content of the food.

As has been stated, sufficient water was added to the food to make it moist. The proportion was 50 cc. water to 100 grams of food until three weeks after the last operation. After this, the quantity was reduced to 25 cc. water per 100 grams of food. The animals appeared not to mind unmoistened or actually dry bread, except dog 3, who had very poor teeth. As a control measure, nine months after the last operation, dogs 3 and 4 were placed on the same food intake they had had in the preoperative period, and the daily fluid intake was again noted.

RESULTS. Observation of the animals used in this experiment over a period of one year has led me to believe that one can get very nearly objective evidence about thirst in dogs. There appears to be little of the psychic element in their drinking. When conditions remain fairly constant, and the dogs are well, this fluid intake varies within the same range month after month, the daily fluctuations being considerable in some animals and small in others. As a rule, the dogs used in this experiment showed no tendency to drink simply because water was offered. This observation was interpreted to mean that they drank because they were thirsty and not from habit.

The accompanying chart shows the fluid intake of dog 4 at intervals over a period of 12 months. Five day averages are recorded and the days of operation have been omitted from the calculations. The observations are typical for the dogs of group I. The water intake of all three dogs showed wide daily variations within certain definite limits. In all, there was a much lower fluid intake in the period immediately following the last operation than in the pre-operative period. A part of this decrease can no doubt be regarded as a direct result of the diminished food intake, but not all of it is to be so considered. To test this point, nine months after the last operation dogs 3 and 4 were again placed on the quantity of food eaten in the pre-operative period, but their fluid intake did not quite return to the pre-operative level. In none of these dogs was there any evidence of an increased desire for water.

The dogs in group II had been used for determinations of basal metabolism, had reached a constant weight, and ate nearly constant amounts of meat and bread with 250 cc. of milk daily. The pre-operative and post-

The quantity of secretion poured out by the glands of the buccal, pharyngeal and nasal mucosa has been measured on dog 7, by collection from an esophageal fistula. When the dog was lying quietly the secretion averaged 8.9 grams of extremely viscid mucus per hour. During sleep the quantity fell as low as 1 gram per hour. Five milligrams of pilocarpine, given subcutaneously, caused a secretion of slightly more than 20 grams in the first half hour after injection. Autopsy of this dog has demonstrated that the removal of the salivary glands had been complete. This work will be described in detail in another paper. The question of hypertrophy of the glands of the buccal mucosa after extirpation of the salivary glands has not yet been investigated.

CONCLUSIONS

Total extirpation of the salivary glands in dogs does not increase their average daily water intake. Therefore it appears improbable that the salivary glands play a major rôle in the thirst mechanism.

After total extirpation of the salivary glands in dogs the buccal mucosa remains in a healthy and remarkably moist condition.

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THE INFLUENCE OF ATROPIN AND PILOCARPIN ON THIRST (VOLUNTARY INGESTION OF WATER)

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The importance of local dryness of the mouth and pharynx as the exciting cause of the sensation of thirst, apart from any general bodily dehydration, has long been a subject of controversy. Cannon (1) states that when he dried up his buccal secretions by means of atropin he definitely experienced thirst. He did not drink, and the thirst disappeared when the atropin effect wore off. L. Mueller (2) reports that his experimental subjects were able to differentiate clearly between thirst and the dryness of the mouth induced by atropin. Siebeck (3) is inclined to agree with E. Meyer (4) that one ought definitely to call the sensation which arises after the administration of atropin, thirst, but admits that in the final analysis it is a question of the definition of the concept "thirst."

The converse of the atropin experiments, namely, attempts to alleviate thirst artificially by inducing a free flow of saliva with pilocarpin, has been reported a number of times. Pack (5) withheld water and food from rabbits for seven days. At the end of that time some of the rabbits were injected with 0.5 cc. of a 1 per cent solution of pilocarpin hydrochloride subcutaneously. When salivation had become profuse, water was offered for one hour. The controls which were given no pilocarpin drank 62 to 137 cc. of water in one hour, while the pilocarpin injected animals drank only 0-25 cc. in the same period of time. Schneider (6), Wiethe (7), and Wisotzki and Eymueller (8) report relief in some cases of post-operative thirst by the use of the sialogogues Cesol and Neucesol. On the other hand, Weir, Larson and Rowntree (9) were unable to relieve thirst in four patients with diabetes insipidus by injections of pilocarpin.

In a recent paper (10) I reported that complete extirpation of the salivary glands in dogs did not lead to an increased fluid intake, and concluded that the salivary glands cannot play as important a rôle in the thirst mechanism as Cannon ascribes to them. I therefore thought it very unlikely that atropin could cause thirst or pilocarpin relieve it simply by changes in the degree of moistness of the mouth. However, the possibility remained that these drugs might affect water ingestion by some other means, as for example, by their effect upon water distribution in the body.

The following experiments were performed in the hope of showing definitely 1, whether atropin and pilocarpin have any influence upon water ingestion, and 2, whether any such effects are related to the presence or absence of a free flow of saliva.

METHODS. In all six dogs were used, three normal animals and three in which the salivary glands had been extirpated. They were placed in metabolism cages in a room where they were not subjected to wide fluctuations of temperature and were fed equal parts of meat and bread. The quantity of food eaten was kept as nearly constant as possible. Water intake and urine were measured. The following experiments were performed on these animals:

A. Experiments with atropin. 1. The effect on water intake of the repeated administration of atropin over a period of three days. Two normal and two operated dogs were used. Control observations were made for eight days preceding and nine days following the administration of the drug. On the three days of the experiment a total of five doses of 0.14 mgm. per kgm. of atropin was given subcutaneously. One dose was given at 2:30 p.m. on the first day, and on the second and third days, injections were made at 10:00 a.m. and 5:00 p.m. The daily water intake and the output in urine and feces were measured.

2. The effect upon the two-hourly water ingestion of atropin in single doses of 2 to 20 mgm. Three normal and two operated dogs were used. On four to five control days the water drunk was measured every two hours from 8:30 a.m. until 6:30 p.m. On the days of the experiment the atropin was given subcutaneously at 10:30 a.m., and the water intake was measured every two hours until 6:30 p.m. The dogs were fed daily at 4:30 p.m.

B. Experiments with pilocarpin. 1. The influence of pilocarpin upon water ingestion after a two day period of water deprivation. Two normal and three operated dogs were used. The water intake was measured for eight days. Then water was withheld for two days, food being given as usual. On the morning of the third day 0.6 to 0.7 mgm. per kgm. of pilocarpin was given subcutaneously, and water was offered. The fluid intake was recorded the second and fourth hours after the injection, and then daily until it returned to the normal level.

2. The effect of pilocarpin upon water ingestion after a two day period of fasting and water deprivation. This experiment was performed in the same way as the preceding one except for the fact that food was withheld as well as water. Two normal and two operated dogs were used. The experiment was performed twice. Each time only one normal and one operated dog were injected with pilocarpin, while the others acted as controls.

RESULTS. **A. Experiments with atropin.** 1. The results of the repeated administration of small doses of atropin over a period of three days are

presented in table 1. In only one instance (dog 10) was the average water intake greater during the experimental than during the control period. The average increase of 15 cc. appears to be insignificant because the daily intake during the experimental period remained within the limits of the daily fluctuation observed during the control period.

2. When single large doses of atropin were administered in the morning to dogs with and without salivary glands the effect upon the two-hourly intake of water throughout the day shows no change indicative of the production of thirst as a result of the injection. Doses of 5 mgm. were given on two days, a dose of 10 mgm. on one day and finally 20 mgm. on three days. Between experimental days, time was given for recovery from the effect of the drug. Since the results obtained with the smaller

TABLE 1

The influence upon water intake of repeated small doses of atropin over a period of 3 days

	NORMAL DOGS						DOGS WITHOUT SALIVARY GLANDS					
	Dog 8, weight 13.8 kgm.			Dog 10, weight 10.6 kgm.			Dog 3, weight 10.9 kgm.			Dog 4, weight 11.4 kgm.		
	Food	Water drunk	Water in urine and feces	Food	Water drunk	Water in urine and feces	Food	Water drunk	Water in urine and feces	Food	Water drunk	Water in urine and feces
	gram	cc.	cc.	gram	cc.	cc.	gram	cc.	cc.	gram	cc.	cc.
Control period, average 8 days.....	400	155	202	365	230	148	285	157	147	400	200	169
Experimental period, average 3 days.....	400	153	226	390	245	143	300	140	90	400	173	307
Control period, average 9 days.....	400	200	231	370	225	165	300	170	113	400	166	234

dosages are in every way comparable with the effects of the 20 mgm. dose, the observations of the latter alone are given in detail in table 2.

It will be seen that in the case of a single dog without salivary glands (dog 3) the average ingestion of water was considerably greater during the two hours following the injection than in the same two hours during the control period. An increase at the same hour was observed in this same dog in one instance after a 5 mgm. dose of atropine. In all other cases the fluid intake during this period was lower than usual. Minor fluctuations up or down were noted during the next four hours up to the time of feeding. The total intake for 24 hours was higher after atropin in three dogs (two with and one without salivary glands) and lower in two dogs (one with and one without salivary glands). The daily fluctuations were within normal limits. No difference in the behavior of the two groups of

animals was observed which could be interpreted as meaning that atropin produced an increased desire for water by inhibiting salivary secretion and increasing the local dryness of the mouth.

B. *Experiments with pilocarpin.* 1. The results of administering a fairly large dose of pilocarpin to normal and operated dogs after having deprived them of water for a period of two days are recorded in table 3. Far from being relieved of thirst by the free flow of saliva which pilocarpin induced, the normal dogs drank more water during the first four hours after injection and also during the 24 hour period. The emetic action of

TABLE 3

The influence of pilocarpin upon water intake after a two day period of water deprivation

	OPERATED			NORMAL	
	Dog 3, weight 10.9 kgm.	Dog 4, weight 11.4 kgm.	Dog 7, weight 7.3 kgm.	Dog 8, weight 13.8 kgm.	Dog 10, weight 10.6 kgm.
Pilocarpin.....	7 mgm.	7 mgm.	5 mgm.	10 mgm.	7 mgm.
	cc.	cc.	cc.	cc.	cc.
Control period (average of 8 days):					
Water drunk.....	156	174	100	190	215
Water in urine and feces.....	120	187		195	145
Water only withdrawn for 2 days; pilocarpin given on third day:					
Water taken in					
First and second hour.....	140	165	180	295	300
Third and fourth hour.....	105	90	0	205	155
Twenty-four hours.....	385	425	305	830	755
Water in urine, feces, vomitus.....	100	150		465	300
Vomiting.....	None	Slight	Slight	Moderate	Marked
Salivation.....	0	0	0	++	+++

the pilocarpin appeared to be more marked in the case of the normal animals. The amount of fluid ingested minus vomitus and urine is of the same order of magnitude in the two groups of animals.

2. In this experiment only two of the four animals used were injected at the same time. The other two acted as controls. See table 4. In the first experiment one notes that the dogs, normal and operated alike, which received pilocarpin, drank more than the other two dogs during the height of the pilocarpin effect. In the second experiment, dog 3, an operated dog which received pilocarpin, drank less during the first hour than dog 4

(also operated), which had not received pilocarpin. However, in the case of the normal dogs, no. 11, which had received pilocarpin, drank more than no. 10, which had not.

Comparing the reactions of the individual dogs in the two experiments we see that one of the dogs without salivary glands (no. 3) drank less when pilocarpin was injected after a period of thirst than when the drug was not

TABLE 4

The influence of pilocarpin upon water intake after withdrawal of food and water for a period of two days

	OPERATED		NORMAL		OPERATED		NORMAL	
	Dog 3	Dog 4	Dog 10	Dog 11	Dog 3	Dog 4	Dog 10	Dog 11
Pilocarpin dosage.....	0 mgm.	7 mgm.	7 mgm.	0 mgm.	7 mgm.	0 mgm.	0 mgm.	8 mgm.
	Average of 10 days				Average of 3 days			
	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.
Control period:								
Water drunk.....	255	253	241	239	213	195	195	302
Water in urine and feces.....	125	368	182	198	171	310	150	198
Food and water withdrawn for 2 days; pilocarpin, food and water given on third day								
Water drunk:								
First hour.....	260	360	330	240	105	130	60	310
Second hour.....	0	0	0	0	5	50	0	250
Third and fourth hour.....	0	0	0	0	60	35	30	80
In 24 hours.....	690	695	790	535	540	395	370	1,020
Urine.....	35	230	100	200	150	300	275	
Vomiting.....	0	Slight	380	0	Slight	0	0	470
Salivation.....	0	0	+++	0	0	0	0	+++

given. The other dogs all drank more. These experiments show that in spite of the variations in the reaction of individual dogs to injections of pilocarpin, no evidence whatsoever has been obtained to show that pilocarpin relieves thirst by promoting a free flow of saliva. The only dog which drank a smaller quantity of water after an injection of pilocarpin was one which had been deprived of salivary glands.

CONCLUSIONS

1. Repeated injections of small doses of atropin over a period of three days did not significantly alter the water intake of dogs with or without salivary glands.

2. Large single doses of atropin (up to 20 mgm.) did not significantly alter the two-hourly fluid intake of these dogs.

3. Injections of pilocarpin, after a two day thirst period, did not diminish the water intake of normal dogs as compared with that of dogs which had been deprived of their salivary glands.

4. It, therefore, appears likely that whatever changes in water ingestion may occur after injections of atropin or pilocarpin are caused by some other factor than drying or moistening of the mucous membranes of the mouth and pharynx by suppression of or increase of the salivary secretion.

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